

Associations of Coffee Drinking and Cancer Mortality in the Cancer Prevention Study-II

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Abstract

Background: Associations of coffee consumption with cancer mortality are inconsistent for many types of cancer, and confounding by smoking is an important concern.

Methods: Cox proportional hazards regression was used to estimate multivariable-adjusted HRs for coffee consumption associated with death from all cancers combined and from specific cancer types among 922,896 Cancer Prevention Study-II participants ages 28–94 years who completed a four-page questionnaire and were cancer free at baseline in 1982.

Results: During follow-up through 2012, there were 118,738 cancer-related deaths. There was a nonlinear association between coffee consumption and all-cancer death among current smokers and former smokers and no association among never smokers. Among nonsmokers, a 2 cup/day increase in coffee consumption was inversely associated with death from colorectal [HR = 0.97; 95% confidence interval (CI) 0.95–0.99], liver [HR = 0.92; 95%

CI, 0.88–0.96], and female breast (HR = 0.97; 95% CI, 0.94–0.99) cancers, and positively associated with esophageal cancer–related death (HR = 1.07; 95% CI, 1.02–1.12). For head and neck cancer, a nonlinear inverse association was observed starting at 2–3 cups per day (HR = 0.72; 95% CI, 0.55–0.95), with similar associations observed at higher levels of consumption.

Conclusions: These findings are consistent with many other studies that suggest coffee drinking is associated with a lower risk of colorectal, liver, female breast, and head and neck cancer. The association of coffee consumption with higher risk of esophageal cancer among nonsmokers in our study should be confirmed.

Impact: These results underscore the importance of assessing associations between coffee consumption and cancer mortality by smoking status. *Cancer Epidemiol Biomarkers Prev*; 26(10): 1477–86. ©2017 AACR.

Introduction

Approximately half of American adults report daily coffee consumption (1); thus, the potential health benefits and risks of drinking coffee are of considerable public health interest. There is substantial evidence of an inverse association between coffee drinking and all-cause mortality (2, 3). However, associations with cancer-related death overall and with death from specific types of cancer are unclear. In 1991, an expert working group convened by the International Agency for Research on Cancer (IARC) classified coffee as "possibly carcinogenic to humans" based on limited evidence that coffee drinking might be a cause of urinary bladder cancer (4). Twenty-five years later, another IARC working group evaluated a substantially larger body of evidence, including from well-conducted prospective studies, and found the evidence on the carcinogenicity of coffee drinking to be "unclassifiable," and that coffee drinking is not a cause of female breast, pancreas, and prostate cancers, but may reduce risk of uterine

endometrium and liver cancers (5). The evidence was judged to be inadequate for all other cancer types, including bladder cancer (5). Reasons for the lack of convincing evidence included epidemiologic study design issues, residual confounding by smoking, and inconsistent results.

Prospective studies are needed that focus on coffee consumption in relation to risk of cancer-related death, particularly with specific types of cancers for which the evidence is considered inadequate. In addition, because coffee consumption is often associated with smoking, studies are needed that carefully assess confounding by smoking through stratification on smoking status and/or statistical adjustment for detailed smoking history data. The American Cancer Society's (ACS) Cancer Prevention Study-II (CPS-II) is a nationwide, prospective cohort study of 1.2 million men and women initiated in 1982 when self-reported coffee consumption, smoking history, and other information were collected. This cohort provides an opportunity for a comprehensive analysis, with detailed control for smoking dose and duration, of the associations of coffee drinking with cancer-related death.

Materials and Methods

Study population

Enrollment and data collection procedures for CPS-II were reported previously (6). Briefly, in 1982, nearly 1.2 million adults ages 28 years and older were enrolled by ACS volunteers in all 50 U.S. states, the District of Columbia, and Puerto Rico, and completed a four-page questionnaire. CPS-II is approved by the Institutional Review Board of Emory University (Atlanta, GA).

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Participants were excluded from this analysis if on the baseline questionnaire they reported: a personal history of cancer other than nonmelanoma skin cancer ($n = 82,324$), no information on consumption of any beverage type ($n = 28,493$), uninterpretable ($n = 5,216$) or implausibly high (i.e., ≥ 20 cups/day) current coffee intake ($n = 3,383$), and former coffee consumption ($n = 34,537$), because results from this group might be biased due to reverse causality (i.e., people stop drinking coffee because they have undiagnosed cancer). Also excluded were participants with uninterpretable smoking information ($n = 63,345$), and those whose smoking history did not fit well into the three major categories used in smoking-stratified analyses (never smokers, former cigarette smokers, or current cigarette smokers), specifically those who had never smoked cigarettes but reported ever cigar/pipe use ($n = 38,427$), and former cigarette smokers who reported current cigar/pipe use ($n = 5,251$). In addition, women whose age at enrollment was ≥ 95 years and men whose age at enrollment was ≥ 90 years were excluded ($n = 482$). Most analyses included 922,896 participants (385,765 men and 537,131 women). Women who reported hysterectomy ($n = 175,800$) were excluded from the endometrial cancer-related death analysis and women who reported hysterectomy or removal of their ovaries ($n = 186,569$) were excluded from the ovarian cancer-related death analysis.

Assessment of coffee consumption

The baseline questionnaire included demographic and other factors, as well as a detailed history of current and past use of cigarettes (and in men cigars, pipes, and smokeless tobacco). The question: "How many cups, glasses or drinks of these beverages do you usually drink a day, and for how many years?" was used to assess the frequency and duration of consumption of various beverages. If consumption changed in the 10 years prior to enrollment, participants were asked to record their previous consumption for each beverage type. If intake was less than once a day, but at least three times a week, participants were instructed to write "1/2." Caffeinated and decaffeinated coffee consumption were reported separately.

Never coffee drinkers were defined as participants who wrote zero or left blank the amount for current and previous consumption for caffeinated and decaffeinated coffee but did report consumption of other beverages. Former coffee drinkers were participants who wrote zero or left blank the amount for current intake but did provide information on previous amount. Current coffee consumption was based on the daily amount reported.

Mortality follow-up for cause of death

From 1982 through 1988, vital status of CPS-II participants was ascertained by ACS volunteers who directly contacted their enrollees, and they recorded the dates and places of deaths. Reported deaths were verified by obtaining death certificates, and underlying cause of death was recorded by a trained nosologist. Subsequently, linkage to the National Death Index (NDI) was used to identify deaths, and cause of death, that occurred from 1989 through 2012. Underlying cause of death has been determined for over 99% of all known deaths. For this analysis, the specific outcomes of interest are underlying cause of death from all cancers [International Classification of Disease (ICD)-9 codes 140-209; ICD-10 codes C00-C97; refs. 7, 8)], as well as death from specific cancer types (ICD codes shown in Table 3).

Statistical analysis

Follow-up time was from completion of the baseline questionnaire until date of death or December 31, 2012, whichever came first. Follow-up time was censored at age 90 years for men and 95 years for women because a small percentage of deaths are missed by NDI linkage, which could result in misclassification of vital status at very advanced ages (9).

Cox proportional hazards regression (10) was used to compute HRs and 95% confidence intervals (CI) for associations of coffee consumption and risk of cancer-related deaths. For death from all-cancers combined, coffee consumption was classified as never coffee drinkers (reference group), and six categories of current daily coffee consumption ($>0-1$, $2-3$, $4-5$, $6-7$, $8-9$, and ≥ 10 cups per day). For death from specific cancer types, the highest category of coffee consumption was usually 6 or more cups per day. Coffee consumption also was modeled as a continuous variable where never drinkers were assigned 0 cups/day and restricted cubic spline models (11) were used to test for nonlinearity. All models were stratified on single year of age, and, if appropriate, adjusted for sex. Confounding by smoking was examined by including in the model dummy variables for smoking history [never smoker (reference); former cigarette smokers subcategorized by time since quitting (<10 , $10-20$, or ≥ 20 years) and number of cigarettes smoked per day (<20 , 20 , or ≥ 20), or as a separate category, former smokers with missing information on time since quitting and/or cigarettes per day; and current cigarette smokers subcategorized by combinations of duration of smoking (<30 , $30-39$, or ≥ 40 years) and number of cigarettes smoked per day (<20 , $20-29$, or ≥ 30), or as a separate category, current smokers with missing information on time since quitting and/or cigarettes per day]. Models including only former smokers, or only never and former smokers, were still adjusted for combinations of duration and cigarettes per day as described above. Full multivariable-adjusted models included race, marital status, education, alcohol intake, body mass index, physical activity, family history of cancer, red/processed meat and vegetable intake, and current tea intake, as defined in Table 1, with additional categories for missing data. Oral contraceptive use, postmenopausal estrogen use, menopausal status, parity, and age at first birth did not confound associations of coffee consumption with death from female breast, endometrial, ovarian, or cervical cancers. Therefore, these factors were not included in final models. Multivariable-adjusted associations of decaffeinated coffee and caffeinated coffee consumption modeled as continuous variables in relation to death from specific cancer types were computed with mutual adjustment.

The proportional hazards assumption was assessed using likelihood ratio tests by comparing multivariable-adjusted models with and without cross-product terms for follow-up time and coffee consumption. Similarly, likelihood ratio tests were used to test for multiplicative interactions of never and former smoking status on the associations of coffee consumption with risk of death from specific cancer types. All analyses were performed using Statistical Analysis Software (SAS) version 9.2 (SAS Institute Inc.).

Results

Distribution of sociodemographic lifestyle and other factors by coffee consumption

At study baseline, 14.7% of participants were never coffee drinkers. Mean age was lower across higher levels of current coffee

Table 1. Baseline characteristics by coffee consumption among men and women, CPS-II

Characteristics ^a	Current coffee consumption (cups/day)						
	Never (n = 135,287)	>0-1 (n = 193,350)	2-3 (n = 325,037)	4-5 (n = 155,023)	6-7 (n = 71,090)	8-9 (n = 20,519)	≥10 (n = 22,590)
Age (y) mean (SD)	55.2 (11.9)	58.3 (11.2)	56.7 (10.2)	54.9 (9.2)	55.3 (9.4)	53.6 (8.5)	53.2 (8.8)
Sex (%)							
Women	59.5	61.5	59.5	55.1	53.3	52.0	45.9
Men	40.5	38.5	40.5	44.9	46.7	48.0	54.1
Self-reported race (%)							
White	90.0	90.2	95.3	96.8	96.3	97.4	96.9
Black	7.4	6.9	2.7	1.5	1.9	1.1	1.3
Marital status (%)							
Married	81.9	80.3	84.5	86.5	85.7	86.9	86.5
Single	4.7	3.7	3.0	2.7	2.7	2.3	2.3
Separated or divorced	4.6	4.2	3.9	4.2	4.3	4.8	5.3
Widowed	8.0	11.1	8.1	6.2	6.8	5.6	5.4
Attained education (%)							
<High school	14.4	16.8	12.2	11.0	13.5	12.0	14.5
High school graduate	26.5	26.4	26.1	26.1	26.7	26.8	27.0
Some college/trade	27.9	27.5	29.5	30.3	30.1	31.9	31.1
College graduate/more	29.6	27.8	31.1	31.6	28.7	28.4	26.5
Smoking status (%)							
Never smoker	65.7	53.8	43.5	33.6	30.2	22.7	18.9
Former cigarette	19.6	29.2	34.0	33.7	31.0	29.2	26.1
Current cigarette	14.7	17.0	22.5	32.8	38.8	48.1	55.0
Alcohol consumption (%)							
Never drinker	68.9	56.4	47.1	44.0	44.5	45.8	46.2
Former drinker	1.1	1.5	1.5	1.9	2.2	2.8	3.4
<Daily drinker	7.4	12.4	13.9	14.9	13.7	14.3	12.8
1 drink/day	2.8	4.7	6.6	6.7	5.4	5.5	4.9
≥2 drinks/day	6.3	7.9	13.6	15.0	15.2	14.7	15.5
Body mass index (kg/m ² ; %)							
<18.5	2.1	2.0	1.8	1.8	1.9	1.9	2.0
18.5–24.9	47.0	49.2	51.3	50.9	49.8	50.9	48.6
<25–29.9	34.8	34.9	35.3	36.2	36.7	36.3	37.7
≥30	13.5	11.5	9.8	9.3	9.8	9.3	10.0
Physical activity (%)							
None	2.4	2.5	1.9	1.9	2.1	2.2	2.5
Slight	22.4	22.4	23.4	24.2	23.9	25.2	25.2
Moderate	63.8	65.4	65.9	64.6	63.8	62.1	60.8
Heavy	9.6	8.2	7.6	8.2	9.1	9.5	10.5
Family history of cancer (%)							
No	63.4	61.0	59.3	59.7	59.7	59.3	60.6
Yes	36.6	39.0	40.7	40.3	40.3	40.7	39.4
Red/processed meat and vegetable intake (times/week; %)							
≤6.5/>13.5	22.3	23.3	25.3	23.6	21.2	19.2	16.7
≤6.5/≤13.5	27.2	28.9	22.6	20.5	20.1	18.9	18.6
>6.5/>13.5	18.9	18.4	22.8	25.0	25.7	27.2	27.1
>6.5/≤13.5	21.5	19.8	21.2	23.4	25.6	28.0	30.7
Current tea drinker (%)							
No	49.8	40.5	46.8	54.2	56.2	62.3	62.8
Yes	50.2	59.5	53.2	45.8	43.8	37.7	37.2

^aFor some characteristics, column percentages might not add to 100 because of missing data.

consumption (Table 1). Compared with never drinkers, current heavy coffee drinkers (≥10 cups/day) were more likely to be men, white, married, current or former smokers, alcohol drinkers, nondrinkers of tea, and to consume a diet high in red and processed meat and low in vegetables.

Association between coffee consumption and death from all cancers

Among the 922,896 participants in this study, 118,738 died of cancer during 21,568,314 person-years of follow-up time. In age and sex-adjusted analyses of the total cohort, there was a significant positive association between coffee consumption and risk of death from all cancers (Table 2). Most, though not all, of this association was eliminated by adjustment for smoking dose and

duration; inclusion of other risk factors in the model had minimal impact on the HRs. In multivariable-adjusted analyses stratified on smoking status, there was no association between coffee consumption and risk of death from all cancers among never smokers. Among former smokers, the association between coffee consumption and risk was nonlinear, with no clear pattern of association in the categorical multivariable-adjusted analysis. Among current smokers, the positive association between coffee consumption and death from cancer was attenuated after adjustment for smoking history, but remained statistically significant even after further adjustment for other factors. Much of the association between coffee consumption and total cancer death among current smokers was due to lung cancer (HR = 1.04; 95% CI, 1.03–1.05 per two cups/day increase).

Table 2. Associations of coffee consumption with deaths from all-cancers overall and stratified on smoking status, CPS-II, 1982–2012

	Current coffee consumption (cups/day)						Per 2 cups/day (n = 922,896)
	>0-1 (n = 193,350)	2-3 (n = 325,037)	4-5 (n = 155,023)	6-7 (n = 71,090)	8-9 (n = 20,519)	≥10 (n = 22,590)	
Total cohort							
Deaths, n	14,737	41,508	21,546	10,696	3,369	3,895	
Age, sex adjusted mortality rate	529.2	583.2	637.0	706.3	796.2	844.0	
Age, sex adjusted HR (95% CI)	1.00	1.02 (1.00–1.04)	1.20 (1.17–1.22)	1.33 (1.30–1.36)	1.53 (1.47–1.58)	1.65 (1.59–1.71)	1.09 (1.09–1.10) ^c
Age, sex, smoking adjusted HR (95% CI) ^a	1.00	0.97 (0.95–0.99)	0.94 (0.93–0.97)	0.98 (0.92–0.96)	1.01 (0.98–1.05)	1.03 (0.99–1.06)	1.00 (1.00–1.01) ^c
Multivariable-adjusted HR (95% CI) ^b	1.00	0.96 (0.95–0.98)	0.96 (0.94–0.98)	0.99 (0.97–1.02)	1.03 (0.99–1.07)	1.04 (1.00–1.08)	1.01 (1.00–1.01) ^c
Never smoker							
Deaths, n	7,928	13,337	4,965	2,002	414	388	
Age, sex adjusted mortality rate	414.2	402.8	404.8	402.2	381.0	414.8	
Age, sex adjusted HR (95% CI) ^a	1.00	0.98 (0.95–1.01)	0.98 (0.95–1.02)	0.95 (0.91–1.00)	0.95 (0.86–1.05)	0.98 (0.89–1.09)	0.99 (0.98–1.00) ^c
Multivariable-adjusted HR (95% CI) ^b	1.00	0.96 (0.94–1.01)	0.99 (0.95–1.03)	0.95 (0.91–1.00)	0.96 (0.86–1.05)	0.98 (0.88–1.08)	0.99 (0.98–1.00)
Former cigarette							
Deaths, n	3,312	14,370	6,691	2,941	829	838	
Age, sex adjusted mortality rate	567.6	543.2	526.9	557.5	588.6	600.0	
Age, sex adjusted HR (95% CI)	1.00	0.96 (0.90–0.98)	0.95 (0.91–0.99)	1.01 (0.96–1.06)	1.10 (1.02–1.19)	1.12 (1.04–1.21)	1.02 (1.01–1.03) ^c
Age, sex, smoking adjusted HR (95% CI) ^a	1.00	0.94 (0.90–0.98)	0.91 (0.87–0.95)	0.95 (0.90–1.00)	1.00 (0.93–1.08)	1.01 (0.94–1.09)	1.00 (0.99–1.01) ^c
Multivariable-adjusted HR (95% CI) ^b	1.00	0.95 (0.91–0.99)	0.93 (0.89–0.97)	0.96 (0.91–1.01)	1.02 (0.94–1.10)	1.02 (0.95–1.10)	1.00 (0.99–1.01) ^c
Current cigarette							
Deaths, n	3,497	13,801	9,890	5,753	2,126	2,669	
Age, sex adjusted mortality rate	1037.3	1008.3	1029.4	1122.0	1178.7	1181.7	
Age, sex adjusted HR (95% CI)	1.00	0.93 (0.89–0.97)	0.99 (0.92–0.99)	1.07 (1.03–1.12)	1.13 (1.07–1.19)	1.16 (1.10–1.22)	1.04 (1.03–1.05) ^c
Age, sex, smoking adjusted HR (95% CI) ^a	1.00	0.96 (0.92–1.00)	0.94 (0.91–0.98)	0.99 (0.90–0.97)	1.01 (0.96–1.07)	1.01 (0.96–1.07)	1.01 (1.00–1.02) ^c
Multivariable-adjusted HR (95% CI) ^b	1.00	0.96 (0.92–1.00)	0.96 (0.93–1.00)	1.01 (0.97–1.06)	1.04 (0.98–1.10)	1.04 (0.98–1.09)	1.01 (1.01–1.02) ^c

^aAge, sex, and smoking adjusted models included dummy variables for years since quitting smoking and number of cigarettes smoked per day among former cigarette smokers, and years smoked and number of cigarettes smoked per day among current smokers.

^bMultivariable-adjusted models included age, sex, smoking variables, as well as dummy variables for race, marital status, education, alcohol consumption, body mass index, physical activity, family history of cancer, red and processed meat/vegetable intake, and current tea drinking as shown in Table 1, with additional categories for missing data.

^cRestricted cubic spline analysis showed evidence of a nonlinear association ($P < 0.05$).

Table 3. Associations of coffee consumption and risk of death from specific cancer types among nonsmokers (never and former combined), CPS-II, 1982–2012

Type of cancer death (ICD-10 code)		Never coffee drinker (n = 115,402)	Current coffee consumption (cups/day)				Per 2 cups/day (696,391)
			>0–1 (n = 160,460)	2–3 (n = 251,912)	4–5 (n = 104,232)	≥6 (n = 64,355)	
Head and neck (C00.3–C06, C09–C10, C12–C14, C32)	Deaths, n	83	127	170	71	47	
	HR (95% CI) ^a	1.00	0.92 (0.70–1.22)	0.72 (0.55–0.95)	0.68 (0.49–0.94)	0.68 (0.47–0.98)	0.91 (0.83–0.99) ^b
Esophagus (C15)	Deaths, n	167	231	490	233	183	
	HR (95% CI) ^a	1.00	0.86 (0.70–1.05)	1.01 (0.84–1.21)	1.03 (0.84–1.26)	1.25 (1.00–1.55)	1.07 (1.02–1.12)
Stomach (C16)	Deaths, n	265	408	652	268	165	
	HR (95% CI) ^a	1.00	0.98 (0.84–1.14)	1.04 (0.90–1.20)	1.05 (0.88–1.26)	1.02 (0.83–1.24)	1.02 (0.98–1.07)
Colorectum (C18–C21)	Deaths, n	1,462	2,199	3,345	1,284	769	
	HR (95% CI) ^a	1.00	0.96 (0.90–1.03)	0.95 (0.89–1.01)	0.90 (0.84–0.98)	0.86 (0.79–0.95)	0.97 (0.95–0.99)
Pancreas (C25)	Deaths, n	837	1,282	2,088	879	526	
	HR (95% CI) ^a	1.00	1.01 (0.92–1.10)	1.03 (0.94–1.11)	1.04 (0.94–1.15)	1.02 (0.91–1.14)	1.00 (0.97–1.02)
Liver or intrahepatic bile duct (C22)	Deaths, n	272	384	613	233	158	
	HR (95% CI) ^a	1.00	0.93 (0.79–1.09)	0.87 (0.75–1.01)	0.75 (0.62–0.89)	0.79 (0.65–0.97)	0.92 (0.87–0.96)
Gall bladder/extrahepatic bile duct (C23–C24)	Deaths, n	100	178	254	108	71	
	HR (95% CI) ^a	1.00	1.14 (0.89–1.46)	1.07 (0.85–1.36)	1.15 (0.87–1.52)	1.23 (0.90–1.68)	1.03 (0.96–1.10)
Lung, bronchus or trachea (C33–C34)	Deaths, n	1,158	2,147	3,975	2,010	1,409	
	HR (95% CI) ^a	1.00	0.99 (0.93–1.07)	1.01 (0.94–1.08)	1.10 (1.02–1.19)	1.15 (1.06–1.25)	1.04 (1.02–1.06)
Melanoma (C43)	Deaths, n	223	282	515	226	144	
	HR (95% CI) ^a	1.00	0.91 (0.76–1.09)	0.96 (0.81–1.12)	0.95 (0.78–1.14)	0.99 (0.80–1.23)	1.00 (0.95–1.05)
Kidney or other urinary organs (C64–C66, C68)	Deaths, n	320	451	690	272	189	
	HR (95% CI) ^a	1.00	0.98 (0.84–1.13)	0.92 (0.81–1.06)	0.84 (0.71–0.99)	0.93 (0.77–1.11)	0.97 (0.93–1.01) ^b
Bladder (C67)	Deaths, n	253	413	662	289	172	
	HR (95% CI) ^a	1.00	0.99 (0.85–1.16)	0.94 (0.81–1.09)	0.95 (0.80–1.13)	0.89 (0.73–1.09)	0.97 (0.93–1.01)
Brain or nervous system (C70–C72)	Deaths, n	338	518	867	369	238	
	HR (95% CI) ^a	1.00	1.07 (0.93–1.23)	1.05 (0.92–1.20)	1.03 (0.89–1.20)	1.10 (0.93–1.31)	1.01 (0.98–1.05)
Non-Hodgkin lymphoma (C82–C86, C88, C90–C91, C96)	Deaths, n	1,265	1,849	2,962	1,240	752	
	HR (95% CI) ^a	1.00	0.98 (0.91–1.06)	0.98 (0.91–1.05)	0.98 (0.91–1.07)	0.98 (0.89–1.07)	1.00 (0.98–1.02)
Leukemia (C92–C95)	Deaths, n	390	685	1,110	491	307	
	HR (95% CI) ^a	1.00	1.13 (1.00–1.28)	1.10 (0.97–1.23)	1.14 (1.00–1.31)	1.17 (1.01–1.37)	1.03 (0.99–1.06)
Breast (C50)	Deaths, n	1,043	1,471	2,239	850	510	
	HR (95% CI) ^a	1.00	0.93 (0.86–1.01)	0.90 (0.83–0.97)	0.87 (0.79–0.95)	0.89 (0.80–0.99)	0.97 (0.94–0.99)
Cervix (C53)	Deaths, n	37	42	78	37	—	
	HR (95% CI) ^a	1.00	0.80 (0.51–1.26)	1.13 (0.75–1.69)	0.84 (0.52–1.35)	—	0.96 (0.84–1.11)
Endometrium (C54–C55)	Deaths, n	231	319	476	181	108	
	HR (95% CI) ^a	1.00	0.88 (0.74–1.05)	0.84 (0.72–0.99)	0.82 (0.67–1.00)	0.84 (0.66–1.06)	0.96 (0.91–1.01)
Ovary (C56)	Deaths, n	340	574	907	383	221	
	HR (95% CI) ^a	1.00	1.09 (0.95–1.24)	1.04 (0.91–1.18)	1.07 (0.92–1.25)	1.07 (0.90–1.27)	1.02 (0.98–1.06)
Prostate (C61)	Deaths, n	981	1,285	2,135	837	551	
	HR (95% CI) ^a	1.00	0.91 (0.84–1.00)	0.93 (0.86–1.01)	0.86 (0.78–0.94)	0.90 (0.81–1.00)	0.98 (0.95–1.00)

^aMultivariable adjusted models included age, sex, smoking variables, as well as dummy variables for race, marital status, education, alcohol consumption, body mass index, physical activity, family history of cancer, red and processed meat/vegetable intake, and current tea drinking as shown in Table 1, with additional categories for missing data.

^bRestricted cubic spline analysis showed evidence of a nonlinear association ($P < 0.05$).

No violations of the proportional hazards assumption were detected among never or former smokers ($P = 0.15$ and 0.20 for interaction with time, respectively). However, there was evidence of a violation among current smokers ($P < 0.001$ for interaction with time), with HRs for coffee increasing over time, consistent with the possibility that heavy coffee drinkers may have been more likely to continue smoking during follow-up than never coffee drinkers, which would result in confounding by continued smoking. To reduce potential confounding by smoking and due to the violation of the proportional hazards assumption, all further analyses were restricted to the 75.5% of participants who were never and former smokers.

Associations of coffee consumption with death from specific cancer types among nonsmokers

Among nonsmokers (Table 3), there were linear, dose-related inverse associations of coffee consumption with risk of death from cancers of the colorectum, liver, and breast. Restricted cubic spline (and categorical) analyses showed evidence of a nonlinear inverse association between coffee consumption and death from head and neck cancer, with lower risk observed starting at 2–3 cups per day (HR = 0.72; 95% CI, 0.55–0.95) and similar associations observed at higher levels of consumption. For kidney cancer, the association with coffee consumption appeared U-shaped in the categorical analysis, although all HRs were less than one and the lowest risk and only statistically significant

HR (0.84; 95% CI, 0.71–0.99) was for 4–5 cups/day compared with never coffee drinkers. Conversely, there was a linear positive association between coffee consumption and risk of death from esophageal cancer. Categorical analyses suggested a positive association between coffee consumption and death from lung cancer (the HRs showed 10% and 15% higher risks for 4–5 and ≥ 6 cups/day, compared with never drinkers). Notably, as shown in Table 3, we found no evidence of an association between coffee consumption and risk of death from bladder cancer, nor from other types of cancer among nonsmokers.

Further analyses compared the associations of coffee consumption with death from specific cancer types between never and former smokers (Table 4). No significant differences were observed for risk of death from most cancer types, including bladder cancer. Consistent with evidence of residual confounding by cigarette smoking among former smokers, coffee consumption was inversely associated with risk of endometrial cancer–related death among former but not among never smokers ($P = 0.01$ for interaction). Similarly, although the P value for interaction between never and former smokers was not statistically significant ($P = 0.19$), the analysis of coffee consumption modeled as a continuous variable showed no association with death from lung cancer among never smokers and a positive association among former smokers.

The associations of caffeinated and decaffeinated coffee consumption with risk of death from most cancer types were not significantly different (Fig. 1), except for death from cancer of the colorectum for which the inverse association was stronger for decaffeinated than for caffeinated coffee consumption ($P = 0.005$ for difference).

Discussion

In this large, prospective study of coffee consumption and cancer-related death, we found evidence of residual confounding by smoking dose and duration among current smokers at baseline, and for some cancers, among former smokers. These results underscore the importance of assessing associations between coffee consumption and cancer mortality by smoking status. This study also shows inverse associations of coffee consumption with risk of death from cancers of the head and neck, colorectum, liver, and female breast, and a positive association with risk of death from esophageal cancer among nonsmokers.

Residual confounding by smoking is a particular concern for specific types of cancer which are strongly smoking-related, and statistical adjustment for smoking might only partly separate the risk of cancer-related death due to smoking from a possible risk due to coffee consumption. For example, an analysis of the NIH-American Association of Retired Persons (NIH-AARP) cohort study showed that coffee consumption was positively associated with lung cancer incidence among current smokers, and among some, but not all, former smokers classified on cigarettes per day, and there was no association among never smokers (12). Similarly, we found a positive association between coffee consumption and lung cancer–related death among current smokers, and among former smokers, but no association among never smokers. For endometrial cancer, which is inversely associated with smoking (13), a World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) systematic literature review reported a "probable" decreased risk associated with increasing coffee consump-

tion; the meta-analysis of seven prospective studies showed a one cup per day increase in coffee consumption was associated with a 7% (95% CI, 0.91–0.96) lower incidence of endometrial cancer (14). However, consistent with our results, in a subsequent analysis of data from the Million Women's Study, coffee consumption was inversely associated with endometrial cancer incidence among former smokers but not among never smokers (15). For bladder cancer, a 1991 IARC expert panel classified coffee as a "probable" carcinogen (4). More recently, a 2013 WCRF/AICR systematic literature review reported a summary RR = 1.02 (95% CI, 0.97–1.06) per 1 cup of coffee per day based a meta-analysis of 11 prospective studies of bladder cancer incidence and/or mortality (exclusion of the two studies of bladder cancer mortality did not change the RR estimate; ref. 16). Furthermore, consistent with our findings, an analysis of data from the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial cohort study showed no association between coffee consumption and bladder cancer incidence (17). Overall, these results suggest that residual confounding by smoking dose and/or duration, even among former smokers may explain previously observed associations of coffee consumption with lung, endometrial cancer, and bladder cancer risk.

Findings from our study contribute to the growing body of evidence that coffee might be associated with reduced risk of several types of cancer. For head and neck cancer, the current and previous (which was based on oropharyngeal cancer only; ref. 18) finding from CPS-II show an inverse association between coffee consumption and mortality. In the current analysis, this association was nonlinear and was similar for 2–3 cups/day and higher categories of consumption. An inverse association is consistent with a meta-analysis of three prospective studies which showed a summary RR = 0.60 (95% CI, 0.30–0.90) for low/moderate consumption compared with non/lowest consumption associated with risk of buccal cavity/pharynx cancer (19). In contrast to the current study findings, a PLCO Cancer Screening Trial cohort study found a null association between coffee consumption and all head and neck cancer incidence in the entire cohort and in never smokers (17).

Coffee consumption also may be inversely associated with risk of colorectal cancer. A 2011 meta-analysis of 15 prospective studies showed high coffee consumption was associated with lower colorectal cancer risk compared with no/low consumption (RR = 0.89; 95% CI, 0.80–0.97; ref. 19). A 2012 NIH-AARP study showed a significant inverse association between coffee consumption and colorectal cancer incidence (20); in that study, the risk associated with ≥ 6 cups/day (RR = 0.80; 95% CI, 0.69–0.94) was similar to our findings for colorectal cancer mortality (RR = 0.86; 95% CI, 0.79–0.95). However, no association between coffee consumption and colorectal cancer incidence was found in the PLCO Cancer Screening Trial cohort (21).

We observed an inverse relationship between coffee consumption and breast cancer mortality (i.e., risk decreased by 3% per 2 cups/day increase) which is consistent with a study of cancer incidence from the European Prospective Investigation into Nutrition and Cancer (EPIC) cohort (22), and a large meta-analysis of 37 studies (i.e., risk decreased by 2% per 2 cups/day increase; ref. 23). However, no association between coffee consumption and breast cancer incidence was observed in the NIH-AARP cohort (24), nor in the PLCO Screening Trial (17).

Table 4. Associations of coffee consumption with risk of death from specific types of cancer among never smokers and among former smokers, CPS-II, 1982-2012

Type of cancer death (ICD-10 code)	Smoking status	Never coffee drinker	Current coffee consumption (cups/day)					P value for interaction
			>0-1	2-3	4-5	≥6	Per 2 cups/day	
Head and neck (C00.3-C06, C09-C10, C12-C14, C32)	Never smoker	1.00	1.16 (0.78-1.73)	0.93 (0.63-1.39)	0.71 (0.44-1.16)	-	0.83 (0.71-0.98)	0.16
	Former smoker	1.00	0.72 (0.48-1.07)	0.57 (0.40-0.83)	0.59 (0.40-0.86)	-	0.94 (0.85-1.04) ^b	
Esophagus (C15)	Never smoker	1.00	0.97 (0.71-1.32)	1.07 (0.81-1.42)	1.26 (0.90-1.78)	1.47 (1.00-2.16)	1.11 (1.02-1.20)	0.21
	Former smoker	1.00	0.74 (0.57-0.97)	0.90 (0.71-1.14)	0.88 (0.67-1.14)	1.08 (0.83-1.42)	1.05 (1.00-1.11)	
Stomach (C16)	Never smoker	1.00	0.97 (0.80-1.17)	0.96 (0.80-1.16)	1.06 (0.83-1.35)	1.02 (0.76-1.35)	1.01 (0.95-1.08)	0.50
	Former smoker	1.00	0.99 (0.75-1.30)	1.13 (0.88-1.45)	1.07 (0.81-1.41)	1.04 (0.77-1.41)	1.03 (0.98-1.09)	
Colorectum (C18-C21)	Never smoker	1.00	0.94 (0.87-1.02)	0.95 (0.87-1.02)	0.89 (0.81-0.99)	0.89 (0.79-1.01)	0.97 (0.94-1.00)	0.68
	Former smoker	1.00	1.01 (0.89-1.14)	0.97 (0.86-1.09)	0.92 (0.81-1.05)	0.85 (0.74-0.98)	0.96 (0.94-0.99)	
Pancreas (C25)	Never smoker	1.00	1.03 (0.92-1.14)	1.04 (0.95-1.15)	1.13 (1.00-1.28)	1.05 (0.90-1.21)	1.02 (0.98-1.05)	0.09
	Former smoker	1.00	0.95 (0.81-1.12)	0.96 (0.82-1.11)	0.91 (0.77-1.07)	0.93 (0.78-1.12)	0.98 (0.94-1.01)	
Liver or intrahepatic bile duct (C22)	Never smoker	1.00	0.88 (0.72-1.08)	0.84 (0.69-1.02)	0.80 (0.63-1.03)	0.73 (0.53-1.00)	0.91 (0.84-0.97)	0.98
	Former smoker	1.00	0.97 (0.75-1.26)	0.90 (0.71-1.14)	0.71 (0.54-0.94)	0.83 (0.62-1.11)	0.92 (0.87-0.98)	
Gall bladder or extrahepatic bile duct (C23-C24)	Never smoker	1.00	1.04 (0.78-1.38)	0.99 (0.75-1.30)	1.07 (0.76-1.51)	1.15 (0.78-1.70)	1.02 (0.93-1.11)	0.65
	Former smoker	1.00	1.60 (0.92-2.78)	1.47 (0.86-2.49)	1.53 (0.87-2.71)	1.64 (0.90-2.99)	1.05 (0.94-1.16)	
Lung, bronchus or trachea (C33-C34)	Never smoker	1.00	1.08 (0.96-1.21)	1.01 (0.90-1.13)	1.16 (1.01-1.33)	1.00 (0.84-1.19)	1.01 (0.98-1.05)	0.19
	Former smoker	1.00	0.95 (0.87-1.05)	1.01 (0.92-1.09)	1.09 (0.99-1.19)	1.17 (1.07-1.29)	1.05 (1.03-1.07)	
Melanoma (C43)	Never smoker	1.00	0.88 (0.71-1.09)	0.94 (0.77-1.15)	0.99 (0.77-1.26)	1.00 (0.75-1.34)	1.02 (0.95-1.09)	0.57
	Former smoker	1.00	1.01 (0.72-1.41)	1.00 (0.74-1.36)	0.94 (0.67-1.31)	1.02 (0.71-1.46)	0.98 (0.91-1.05)	
Kidney, or other urinary organs (C64-C66, C68)	Never smoker	1.00	0.99 (0.83-1.19)	0.94 (0.79-1.12)	0.90 (0.72-1.13)	0.87 (0.66-1.14)	0.95 (0.89-1.01)	0.55
	Former smoker	1.00	0.93 (0.73-1.19)	0.87 (0.70-1.10)	0.77 (0.59-1.00)	0.93 (0.71-1.22)	0.98 (0.91-1.05)	
Bladder (C67)	Never smoker	1.00	0.92 (0.74-1.14)	0.82 (0.67-1.01)	0.98 (0.75-1.27)	0.80 (0.57-1.12)	0.95 (0.88-1.02)	0.57
	Former smoker	1.00	1.07 (0.84-1.37)	1.05 (0.84-1.32)	0.97 (0.76-1.25)	0.97 (0.74-1.27)	0.98 (0.93-1.03)	
Brain or nervous system (C70-C72)	Never smoker	1.00	1.04 (0.88-1.23)	1.10 (0.94-1.28)	1.02 (0.84-1.25)	1.03 (0.81-1.30)	1.01 (0.96-1.06)	0.68
	Former smoker	1.00	1.13 (0.87-1.47)	1.02 (0.80-1.30)	1.06 (0.82-1.38)	1.18 (0.90-1.56)	1.02 (0.97-1.08)	
Non-Hodgkin lymphoma (C82-C86, C88, C90-91, C96)	Never smoker	1.00	1.01 (0.92-1.10)	1.00 (0.92-1.09)	1.06 (0.95-1.17)	0.95 (0.84-1.08)	1.00 (0.97-1.03)	0.86
	Former smoker	1.00	0.93 (0.81-1.06)	0.92 (0.82-1.04)	0.89 (0.77-1.01)	0.97 (0.83-1.12)	1.01 (0.98-1.04)	
Leukemia (C92-C95)	Never smoker	1.00	1.08 (0.93-1.26)	1.02 (0.88-1.18)	1.15 (0.96-1.37)	0.98 (0.79-1.23)	1.00 (0.95-1.05)	0.12
	Former smoker	1.00	1.31 (1.03-1.65)	1.30 (1.04-1.62)	1.28 (1.01-1.62)	1.47 (1.15-1.88)	1.05 (1.00-1.10)	
Breast (C50)	Never smoker	1.00	0.96 (0.87-1.05)	0.92 (0.85-1.00)	0.93 (0.83-1.03)	0.94 (0.82-1.06)	0.98 (0.96-1.01)	0.07
	Former smoker	1.00	0.84 (0.70-1.00)	0.80 (0.68-0.94)	0.71 (0.59-0.85)	0.74 (0.60-0.92)	0.93 (0.89-0.98)	
Cervix (C53)	Never smoker	1.00	0.78 (0.48-1.27)	1.09 (0.70-1.70)	0.80 (0.47-1.37)	-	0.96 (0.82-1.13)	0.84
	Former smoker	1.00	0.81 (0.26-2.53)	1.14 (0.41-3.15)	0.88 (0.29-2.60)	-	0.95 (0.72-1.25)	
Endometrium (C54-C55)	Never smoker	1.00	0.91 (0.75-1.11)	0.88 (0.73-1.06)	0.89 (0.71-1.12)	0.96 (0.74-1.25)	1.00 (0.94-1.06)	0.01
	Former smoker	1.00	0.73 (0.50-1.08)	0.67 (0.47-0.96)	0.58 (0.39-0.88)	0.52 (0.32-0.85)	0.84 (0.75-0.94)	
Ovary (C56)	Never smoker	1.00	1.04 (0.89-1.21)	1.00 (0.86-1.15)	1.09 (0.92-1.29)	1.09 (0.89-1.33)	1.03 (0.98-1.07)	0.52
	Former smoker	1.00	1.39 (1.00-1.93)	1.28 (0.94-1.75)	1.18 (0.84-1.66)	1.17 (0.81-1.70)	1.00 (0.93-1.07)	
Prostate (C61)	Never smoker	1.00	0.93 (0.83-1.04)	0.93 (0.83-1.03)	0.88 (0.76-1.02)	0.90 (0.76-1.08)	0.98 (0.94-1.02)	0.83
	Former smoker	1.00	0.89 (0.78-1.01)	0.92 (0.82-1.04)	0.83 (0.73-0.95)	0.88 (0.76-1.02)	0.98 (0.95-1.01)	

^aMultivariable adjusted models included age, sex, smoking variables, as well as dummy variables for race, marital status, education, alcohol consumption, body mass index, physical activity, family history of cancer, red and processed meat/vegetable intake, and current tea drinking as shown in Table 1, with additional categories for missing data.

^bRestricted cubic spline analysis showed evidence of a nonlinear association ($P < 0.05$).

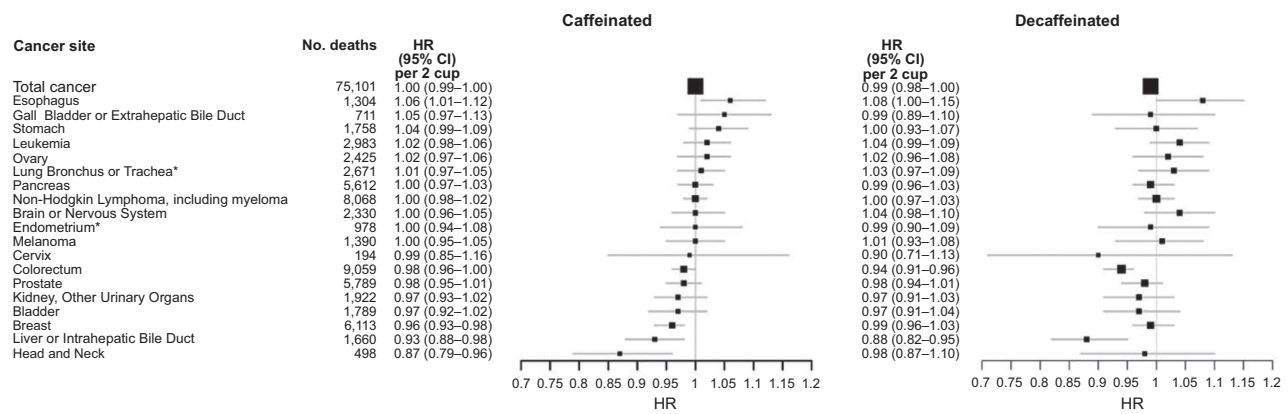


Figure 1.

Caffeinated and decaffeinated coffee consumption and cancer mortality. HRs per 2 cup/day increase among nonsmokers adjusted for age (continuous), sex, years since quitting and number of cigarettes smoked per day among former smokers, race, marital status, education, alcohol, body mass index, physical activity, family history of cancer, red and processed meat/vegetable intake, and current tea drinking; caffeinated and decaffeinated coffee are mutually adjusted. *, Because of concern for residual confounding by smoking dose and duration among former smokers, results for lung, bronchus, and trachea cancer, and for endometrial cancer are shown for never smokers.

In our study, there was a nonlinear inverse association between coffee consumption and death from kidney cancer among nonsmokers, where the lowest risk was for consumption of 4–5 cups/day. However, there was no association between coffee intake and kidney cancer incidence in the PLCO Cancer Screening Trial cohort (17). Furthermore, a 2015 WCRF/AICR systematic literature review of prospective studies showed no association between coffee consumption and kidney cancer risk (25).

Finally, there is growing evidence that coffee consumption is associated with a lower risk of death from liver cancer. Our finding of a 21%–25% lower risk with consumption of 4 or more cups/day is consistent with those of a large pooled analysis including nine prospective studies (26). In the pooled analysis, consumption of more than three cups/day of coffee was associated with 27% lower liver cancer incidence rates compared with nondrinkers and this association was stronger in nonsmokers than smokers (26).

The potential beneficial effects of coffee on head and neck, colorectal, breast, and liver cancer etiology are not completely understood. Roasted coffee is comprised of hundreds of biologically active compounds including caffeine, flavonoids, lignans, and other polyphenols. These and other coffee compounds have been shown to increase energy expenditure, inhibit oxidative damage, regulate genes involved in DNA repair, have antiapoptotic, anti-inflammatory, and antiangiogenic properties, and/or inhibit metastasis (27). There is also evidence that coffee consumption is associated with lower risk of insulin resistance (28) and type II diabetes (29), which have been associated with higher risks of colorectal, liver, breast and endometrial cancer incidence and/or mortality (30, 31).

In CPS-II, coffee consumption, particularly heavy consumption, was associated with a significantly higher risk of death from esophageal cancer, even in never smokers. Although we recognize there are known etiologic differences between squamous cell carcinoma and adenocarcinoma of the esophagus, information on histologic subtype of esophageal cancer was not available, and therefore, we could not examine associations with coffee consumption by histologic type. In a recent

WCRF/AICR systematic literature review of five prospective studies, there was no association between coffee and esophageal cancer risk (32). Notably, no individual study reviewed included more than 340 cases, and power was limited for associations with consumption at high amounts, and for analyses by histologic subtype. The positive association between coffee consumption and esophageal cancer mortality found in our study might be due to chance, or confounding by unknown factors. Alternatively, coffee might increase esophageal cancer risk through an inflammatory mechanism as a result of reflux; however, there is inconsistent evidence on the role of coffee consumption in gastro-esophageal reflux disease, in part, because people with reflux tend to reduce or avoid coffee (33). In addition, although hot (65°C or higher) beverage consumption has been linked to risk of esophageal cancer, it is likely that temperature of coffee consumed by most Americans is not high enough to influence risk (34). Further research is needed to better understand the relationships of coffee consumption with squamous cell carcinoma and adenocarcinoma of the esophagus.

The major strengths of this study include its sample size, availability of detailed exposure and covariate data, a wide-range of coffee consumption, and long-term follow-up which allowed for analyses stratified by smoking status, and by specific cancer types. To our knowledge, this is the largest study to date on coffee consumption and cancer mortality. Although the validity of the information on coffee consumption in CPS-II has not been evaluated directly, the associations found in our study for specific types of cancer are generally similar to those reported in large meta-analyses. In addition, although a single assessment of coffee intake at baseline does not capture changes in consumption during follow-up, any variation over time would likely lead to attenuation of an association. Finally, additional information on types of coffee consumed (e.g., espresso, brewed, drip, or pressed) and on specific cancer subtypes either by histologic subtype (e.g., adenocarcinoma vs. squamous cell carcinoma of the esophagus) or molecular characteristics (e.g., hormone receptor status

of breast cancers) would help to clarify the role of coffee in cancer etiology.

Results from this study demonstrate residual confounding by smoking on the association between coffee consumption and cancer risk particularly among current smokers. Our findings in nonsmokers are consistent with previous studies that found coffee consumption associated with reduced risk of death from head and neck, colorectal, liver, and female breast cancers. However, further research is needed to either confirm or refute our findings of a positive association between coffee consumption and death from esophageal cancer, and to more fully understand the biologic mechanisms underlying associations of coffee and cancer risk.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): S.M. Gapstur

Study supervision: S.M. Gapstur

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